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RESEARCH ARTICLE

Synthesis and Antibacterial Activities of New β-Lactam and Imidazole Derivatives

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Abstract

New ß-lactam, imidazole, oxazole and amide derivatives were synthesized with good yields using simple methodology. Thiosemicarbazide derivatives 2(a-f) were treatment with ethyl chloro acetate to give compounds 1-((arylidene) amino) 2-thioxoimidazolidin-4-one 3(a-f), then3 (a-f) were converted to oxazole derivatives have ß-lactam moiety by reaction with chloro acetyl chloride. Amide derivatives were synthesized by convertion 3(a-f) with acid chloride (acetyl chloride and benzoyl chloride).Structural of all derivatives have been confirmed with IR, H^1 NMR and some of them with mass spectroscopy .These derivatives were tested for invetro antibacterial against *Staphylococcus aureus, Pseudomonasaeruginosa Kelebsiella pneumonia and Escherichia Coli.*Large number of compounds showed high inhibition zone (mm) against different bacterial species.

Keywords: *Imidazole, Oxazole,β-lactam, Amide, Antibacterial activity.*

Introduction

ß-lactam or azetidin- 2- one is an important structural of the penicillin, cephalosporin, carbecephem and cardapenem classes of antibiotics(1). Besides their importance as the key structural component of ß-lactam antibiotics, ß-lactams have been attracting considerable interest in organic synthesis as versatile synthetic intermediates and chiral snthons (2-10).

In addition, the ß-lactam scaffold has found new pharmaceutical applications other than its use as antibiotics such as anticancer agents (11-14) and cholesterol-absorption inhibitors (15). The ring strain of ß-lactam skeleton facilitates ring opening reactions (5, 16, 17, 18) and this unique property has been exploited for the synthesis of different of medicinally active compounds.

There are many reported procedures for the synthesis of ß-lactam, among them Staudinger ketene-imine [2+2] cyclo addition and the chiral ester enolate-imine cyclocondensation(19).

Result and Discussion

The synthetic pathway followed for the synthesis of the title compounds is described in Scheme-1, 2 and 3.Reaction of Aldehyde or Ketone 1 (a-f) with thiosemicarbazide 2. Afforded 2- (arylidene) hydrazine-1-carbothioamide (Schiff's bases) 2(a-f). The IR spectrum of the product collected and recrystallized from ethanol indicated the presence of strong absorption bands between (1583-1627 cm^{-1}) due to (C=N) imine absorption band the evidence that Schiff's bases reaction has occurred.

The 1-((arylidene) amino) 2-thioxoimidazolidin-4-one 3(a-f) was synthesized by the refluxing the 2-(arylidene) hydrazine-1-carbothioamide 2(a-f) with ethyl chloro acetate in alkali media (sodium acetate) in absolute ethanol.

The IR spectrum showed disappearance of the absorption bands of asymmetrical and symmetrical NH_2streching at (3495-3468 cm^{-1}) to compound 2(a) and the presence of the stretching vibration of amide carbonyl group (C=O) appears at (1683 cm^{-1}) to compound 3(a),the evidence that the imidazole ring has occurred.

On the other hand the presence of new absorption bands (2910-2821 cm^{-1}) due to the stretching vibration and bending of (C-H) aliph refers to (CH_2) imidazole ring. Respectively tocompound 3 (a) the evidence that imidazole ring has occurred. The ^1H NMR spectrum to compound 3(a) showed a singlet signal appeared at (11.85) ppm due to one proton of (NH) respectively of imidazole ring ,a singlet singal appeared at (10.01)ppm due to one proton of (OH) phenol group, a singlet signal appeared at (8.27) ppm could be attributed to one proton of (CH=N) group, a doublet signal appeared at (7.60-7.57) ppm integrating for two aromatic proton far away from the (OH) phenol group, a doublet signal appeared at (6.84-6.76) ppm integrating for two aromatic protons near the (OH)phenol group, finally a singlet signal appeared at (4.01-3.87) ppm integrating for two protons of the CH_2 group to imidazole ring . The 4-(3-chloro aryl-4-oxo-1-(3-oxo-5-thioxo-2,3-dihydroimidazo [5,1-b] oxazol-6(5H)-yl) azetidin-2-yl) phenyl- 2- chloroacetate (ß-lactam derivatives) 4(a-b) was prepared by the heating the 1-((arylidene) amino)2-thioxoimidazolidin-4-one 3(a-b) with chloro acetyl chloride in alkali media (Et_3N) in dioxan.

In the IR spectrum compound 4(b) indicated the presence of new absorption band at (1776 cm^{-1}) which is assigned to (C=O) ester group, new absorption band at (1728 cm^{-1}) which is assigned to (C=O) carbonyl group refers to new ß-lactam ring and new absorption band at (1681cm^{-1}) which is assigned to (C=O) carbonyl group refers to new oxazole ring. The disappearance of number of absorption bands to compound 3(b) such as (3225 cm^{-1}) which is assigned to NH group ,(1626 cm^{-1}) which is assigned to (C=N) azomethene group.

The ^1H NMR spectrum compound 4(b) showed adoubet signal appeared at (7.76-7.71) ppm integrating for two protons of the benzene aromatic ring far away ($ClCH_2COO$) group, a doublet signal appeared at (7.28-7.23)ppm integrating for two protons of the benzene aromatic ring near toward ($ClCH_2COO$) group, a singlet signal appeared at (4.53)ppm refers to ($ClCH_2COO$) group interfere with ß-lactam proton, a singlet signal appeared at (4.35)ppm integrating for two protons of the(CH_2) refers to oxazole ring, a singlet signal appeared at (3.75)ppm integrating for one proton of the (=CH-N) refers to imidazole ring , finally a singlet signal appeared at (2.46)ppm integrating for three protons linked with ß-lactam ring. The ((3-chloro aryl)azetidin-1-yl)-5-thioxo-5,6-dihydroimidazo[5,1-b]oxazol-2(3H)-one (ß-lactam derivatives) 5(c-f) was prepared by the heating the 1-((arylidene) amino)2-thioxoimidazolidin-4-one 3(c-f) with chloro acetyl chloride in alkali media (Et_3N) in dioxan. In the IR spectrum compound 5(f) indicated the presence of new absorption band at (1718 cm^{-1}) which is assigned to (C=O) carbonyl group due to new ß-lactam ring and new absorption band at (1683 cm^{-1}) which is assigned to (C=O) carbonyl group due to new oxazole ring. The disappearance of number of absorption bands to compound 3(f) such as (3203 cm^{-1}) which is assigned to NH group ,(3149 cm^{-1}) which is assigned to (CH=N) group,(1839 cm^{-1}) which is assigned to (C=N) azomethene group.

The ^1H NMR spectrum compound 5(f) showed a doublet signal appeared at (7.78-7.75) ppm integrating for two protons of the benzene aromatic ring far away ($N(CH_3)_2$) group, a doublet signal appeared at (6.76-6.73) ppm integrating for two protons of the benzene aromatic ring near toward ($N(CH_3)_2$) group, asinglet signal appeared at (4.86) ppm integrating for two protons of the CH_2 imidazole ring, a singlet signal appeared (4.39)ppm integrating for one proton of the (CH-Cl) due to ß-lactam ring, a singlet signal appeared at (3.79) ppm integrating for one proton of the (CH=) due to imidazole ring, a singlet signal appeared at (3.72) ppm integrating for one proton of the (CH=N) group due to ß-lactam ring , a singlet signal appeared at (2.95)ppm integrating for six proton of the ($N(CH_3)_2$) group, finally the avidence that the compound 5(f) has occurred.

The 4- (((3 -benzoyl-4-oxo-2-thioxoimidazolidin-1-yl) imino) aryl) phenyl benzoate 6 (a-b) was prepared by the refluxing the 1-((arylidene) amino) 2-thioxoimidazolidin-4-one 3 (a-b) with benzoyl chloride in alkali media (Et_3N) in dioxan. In the IR spectrum compound 6(a) indicated the presence of new absorption band at (1728cm^{-1}) which is assigned to (C=O) ester group, new absorption band at (1714cm^{-1}) which is assigned to (C=O) carbonyl group refers to imidazole ring and new absorption band at (1683cm^{-1}) carbonyl amide group linked with imidazole ring,

The disappearance of number of absorption bands to compound 3(a) such as (3227cm^{-1}) which is assigned to (OH) phenol group, (3220cm^{-1}) which is assigned to (NH) imidazole group. The ^{1}H NMR spectrum compound 6(a) showed a singlet signal appeared at (8.37)ppm integrating for one proton of the (CH=N) imine group, signals appeared (8.08-6,66)ppm refers to benzene aromatic rings and a singlet signal appeared at (3.95)ppm integrating for two protons of the (CH_2) imidazole ring the evidence that the compound 6(a) has occurred.

The 3- benzoyl- 1- ((arylidene) amino)-2-thioxoimidazolidin-4-one 7(c-e) was prepared by the refluxing the 1-((arylidene) amino)2-thioxoimidazolidin-4-one 3 (c, d, f) with benzoyl chloride in alkali media (Et_3N) in dioxan. In the IR spectrum compound 7(e) indicated the presence of new absorption band at (1710cm^{-1}) which is assigned to (C=O) carbonyl group refers to imidazole ring and new absorption band at (1685 cm^{-1}) carbonyl amide group linked with imidazole ring, The disappearance of number of absorption bands to compound 3(f) such as (3203cm^{-1}) which is assigned to (NH) imidazole group.

The ^{1}H NMR spectrum compound 7(e) showed a singlet signal appeared at (8.50) ppm integrating for one proton of the (CH=N) imine group, The signals at (7.36-6.65) ppm refers to benzene aromatic rings, a singlet signal appeared at (3.95) ppm integrating for two protons of the (CH_2) imidazole ring and a singlet signal appeared at (3.37) ppm integrating for six protons of the ($N(CH_3)_2$) group, the evidence that the compound 7(e) has occurred.

The 3- benzoyl- 1-((bromobenzylidene) amino)- 2- thioxo-2, 3-dihydro-1H-imidazol-4-yl benzoate 8 (f) was prepared by the refluxing the 1-((arylidene) amino)2-thioxoimidazolidin-4-one 3(e) with benzoyl chloride in alkali media (Et_3N) in dioxan. In the IR spectrum compound 8 (f) indicated the presence of new absorption band at (1726 cm^{-1}) which is assigned to (C=O) carbonyl ester group linked with imidazole ring and new absorption band at (1639 cm^{-1}) carbonyl amide group linked with imidazole ring. The disappearance of absorption band to compound 3(e) such as (3210cm^{-1}) which is assigned to (NH) imidazole group.

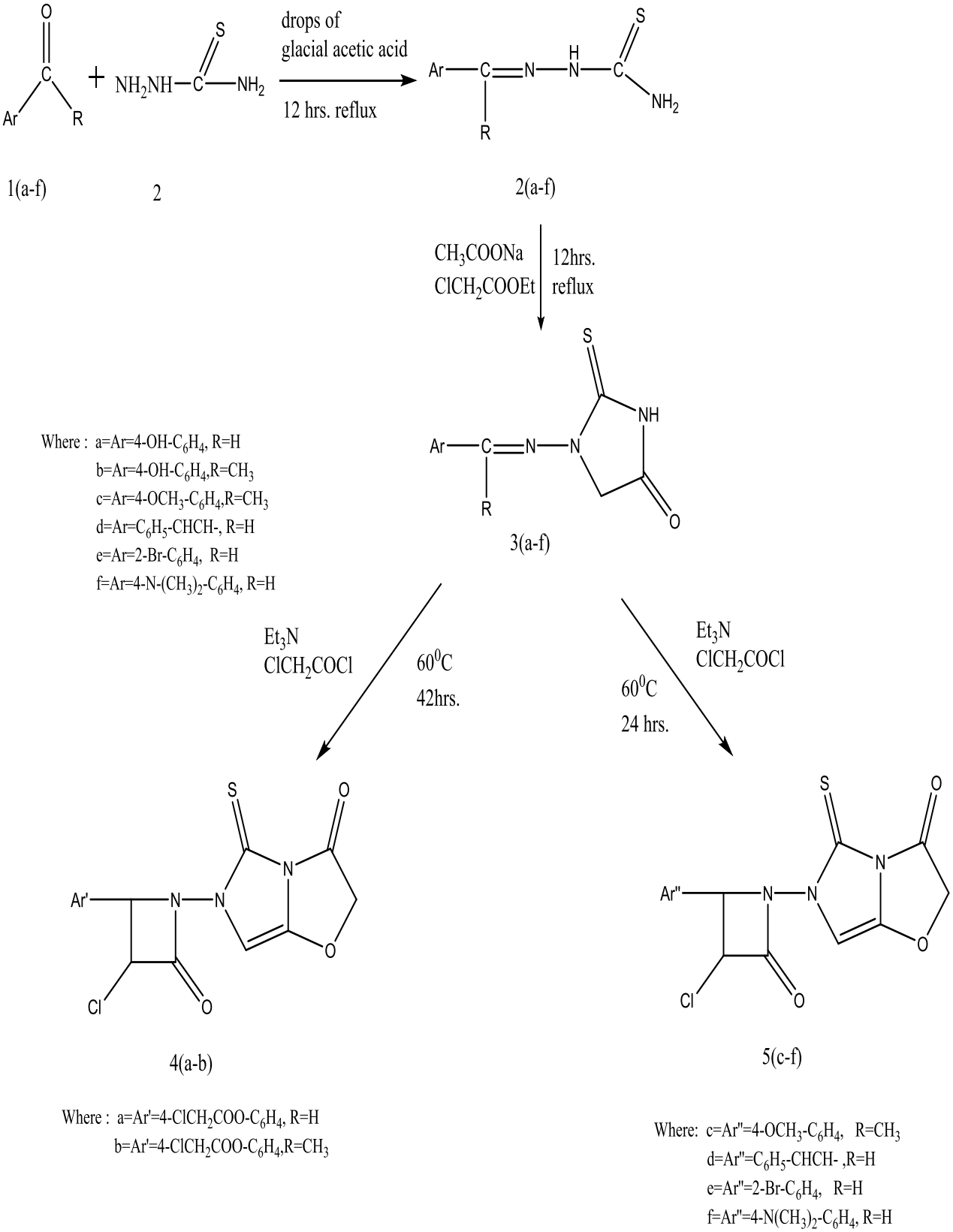
The ^{1}H NMR spectrum compound 8(f) showed a singlet signal appeared at (8.51) ppm integrating for one proton of the (CH=N) imine group. The signals at (7.60-7.31) ppm refers to benzene aromatic rings and a singlet signal appeared at (3.97) ppm integrating for one proton of the (CH=) imidazole ring. The 4-(((3- acetyl- 4- oxo- 2- thioxoimidazolidin-1-yl) imino) aryl) phenyl acetate 9 (a-b) was prepared by the refluxing the 1-((arylidene) amino)2-thioxoimidazolidin-4-one 3(a-b) with Acetoyl chloride in alkali media (Et_3N) in dioxan.

In the IR spectrum compound 9(b) indicated the presence of new absorption band at (1751 cm^{-1}) which is assigned to (C=O) carbonyl ester group, other absorption band at(1714 cm^{-1}) which is assigned to (C=O) carbonyl imidazole ring and new absorption band at (1683cm^{-1}) carbonyl amide group linked with imidazole ring. The disappearance of absorption band to compound 3(b) such as (3308 cm^{-1}) which is assigned to (OH) phenol group and disappearance of absorption band at (3225 cm^{-1}) which is assigned to (NH) imidazole group.

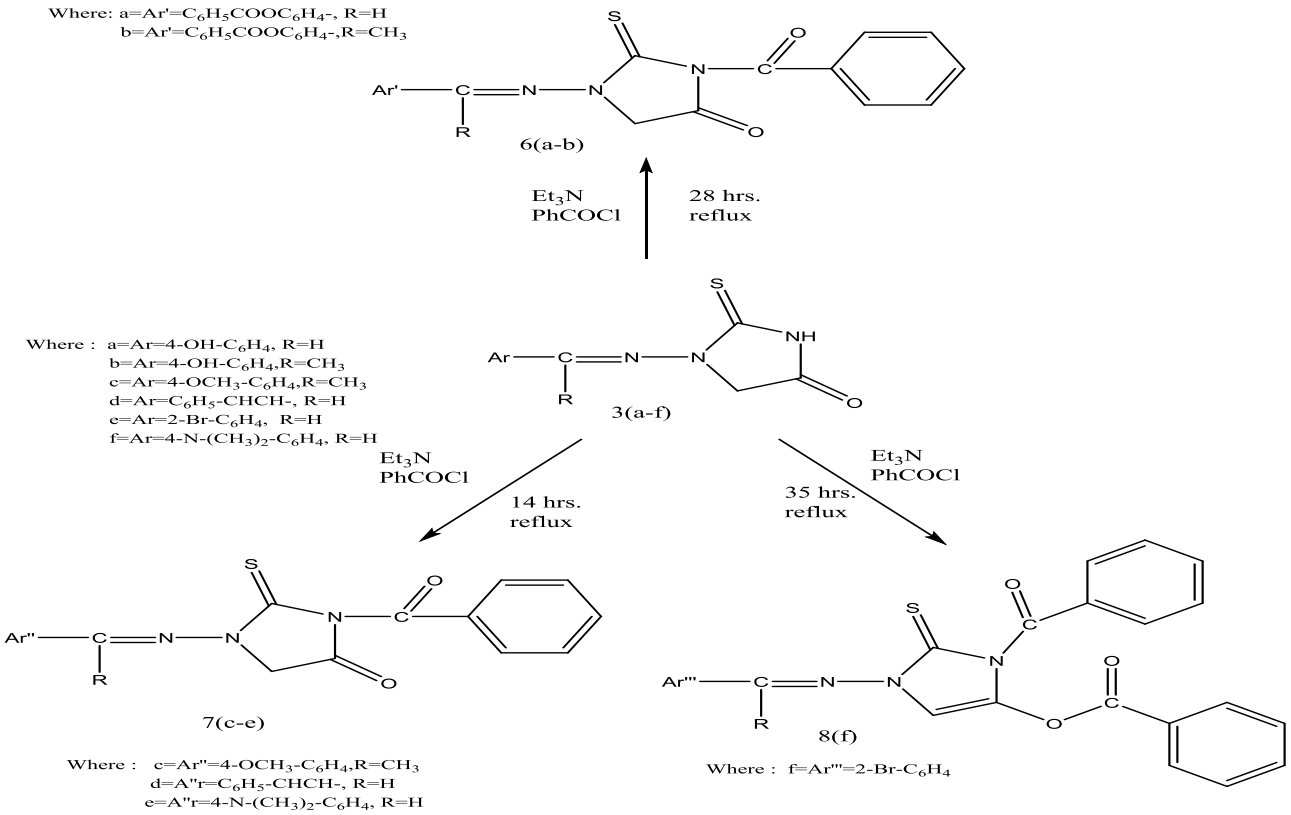
The ^{1}H NMR spectrum compound 9(b) showed a doublet signal appeared at (7.84-7.81)ppm integrating for two protons of the benzene aromatic ring far away from (CH_3COO) group, a doublet signal appeared at (7.18-7.05)ppm integrating for two protons of the benzene aromatic ring near to (CH_3COO) group, a singlet signal appeared at (3.82) ppm integrating for two protons of the (CH_2) imidazole ring, a singlet signal appeared at (2.39) ppm integrating for three protons of the (CH_3COO) group, a singlet signal appeared at (2.26) ppm refers to (CH_3CON) group interfere with ($CH_3C=N$) group.

The 3-acetyl-1-((arylidene) amino)-2-thioxoimidazolidin-4-one 10(c-f) was prepared by the refluxing the 1-((arylidene) amino) 2-thioxoimidazolidin- 4- one 3(c-f) with Acetoyl chloride in alkali media (Et_3N) in dioxan. In the IR spectrum compound 10 (c) indicated the presence of absorption band at (1701 cm^{-1}) which is assigned to (C=O) carbonyl imidazole ring, new absorption band at(1689 cm^{-1}) carbonyl amide group linked with imidazole ring and the disappearance of absorption band to compound 3(c) such as (3236 cm^{-1}) which is assigned to (NH) imidazole group.

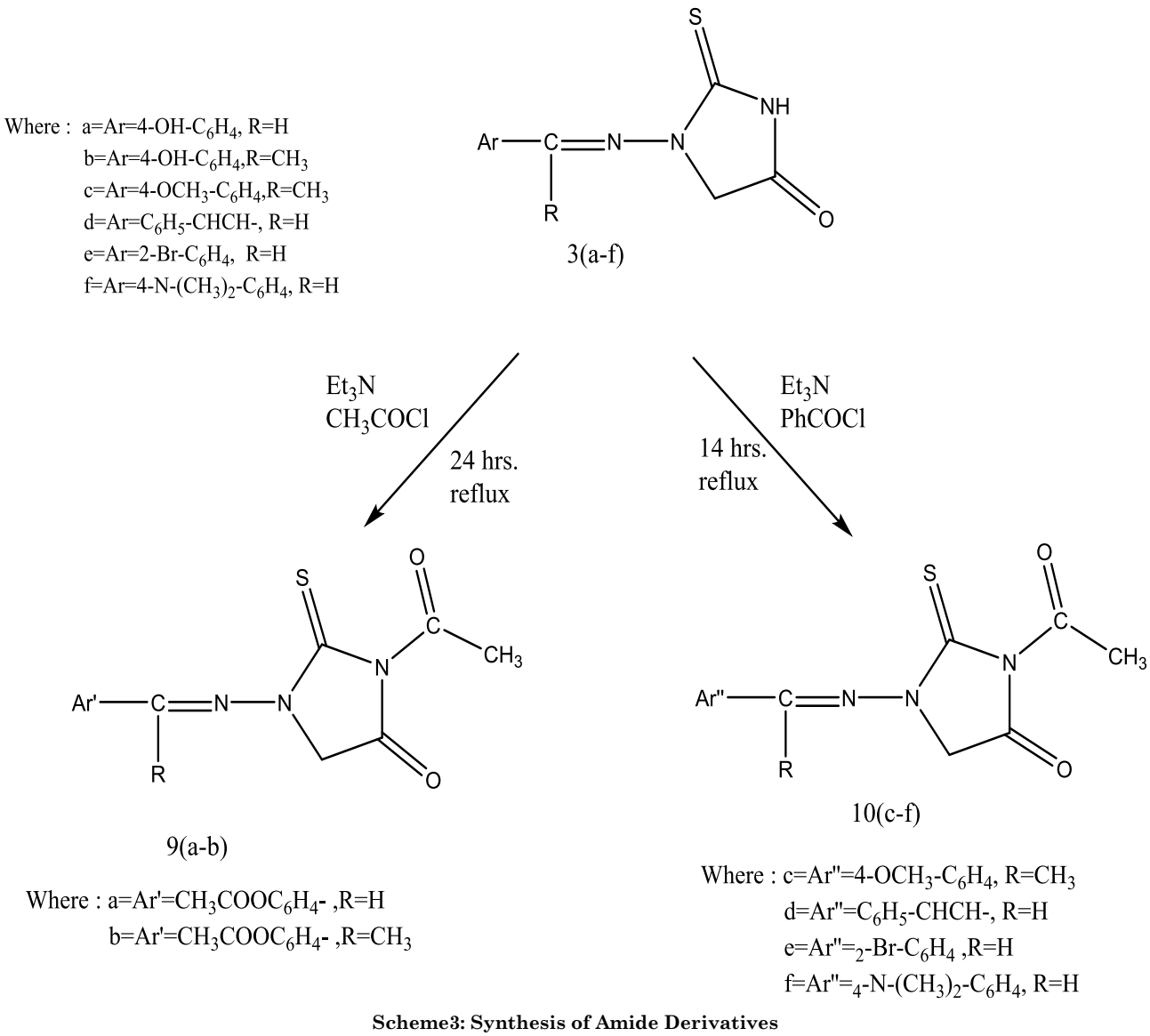
The ^{1}H NMR spectrum compound 10(c) showed a doublet signal appeared at (7.31-7.28)ppm integrating for two protons of the benzene aromatic ring far away from (CH_3O) group, a doublet signal appeared at (6.86-6.83)ppm integrating for two protons of the benzene aromatic ring near to (CH_3O) group, a singlet signal appeared at (4.26)ppm integrating for two protons of the (CH_2) imidazole ring, a singlet signal appeared at (3.67)ppm integrating for three protons of the (CH_3O) linked with benzene ring ,a singlet signal appeared at (2.16)ppm refers to (CH_3CO) group linked with nitrogen imidazole ring and a singlet signal appeared at (1.98)ppm refers to ($CH_3C=N$) group finally the evidence that the compound 10(c) has occurred.



Scheme-1: Synthesis of β-Lactam Derivatives



Scheme-2: Synthesis of Imidazole Derivatives



Scheme3: Synthesis of Amide Derivatives

Antibacterial Activity

The newly synthesized compounds were screened for their antibacterial activity of the agar disc-diffusion method against Staphylococcus aureus, Pseudomona saeruginosa, Kelebsiella pneumonia and Escherichia coli. Dimethylsulphoxide (DMSO) was used as solvent control, and the concentration of tested compound was 10000µg/ml. The results of these studies are summarized in Table 1.

Table 1: Antibacterial Activity of New Compounds

Comp .No. 10000 µg/ml	Inhibition Zone (mm).			
	Gram Positive	Gram Negative		
	Staphylococcus aureus	Pseudomonas aeruginosa	Kelebsiella pneumonia	Escherichia Coli
4(a)	-ve	10	-ve	-ve
4(b)	-ve	25	15	-ve
5(c)	-ve	30	10	-ve
5(d)	20	-ve	25	30
5(e)	20	-ve	30	30
5(f)	-ve	30	-ve	-ve
6(a)	30	-ve	-ve	-ve
6(b)	30	-ve	15	-ve
7(c)	30	-ve	10	-ve
7(d)	20	-ve	25	-ve
7(e)	30	-ve	-ve	-ve
8(f)	15	-ve	25	-ve
9(a)	-ve	-ve	30	-ve
9(b)	-ve	28	24	-ve
10(c)	-ve	-ve	-ve	-ve
10(d)	20	30	30	10
10(e)	20	-ve	30	10
10(f)	-ve	-ve	-ve	-ve
DMSO	-ve	-ve	-ve	-ve

-ve no antibacterial activity

It could be observed that most of the tested compounds showed high inhibition toward staphylococcus aureus, except compounds 4(a),4(b),5(c),5 (f),9 (a),9 (b),10 (c),and 10(f). While the tested compounds showed high inhibition toward Kelebsiella pneumonia ,except compounds 4(a),5 (f),6 (a),7(e), 10(c),and 10(f). But some of the compounds showed high inhibition toward Pseudomonas aeruginosa, like 4(a),4(b),5 (c),5 (f),9 (b),10 (d).While low compounds were active toward E. coli such as5 (d),5 (e),10 (d),and 10(e).In addition the compounds 10(c),and 10(f) have no antibacterial activity.

Experimental

Melting points were determined in open capillaries and are uncorrected on SMP30 melting points (Stuart, Germany). IR spectra were recorded using Fourier Trausform Infra-Red spectrometry (FTIR) spectra in the range (4000-600) cm^{-1} by using ATR technique Shimadzu 8400 S, made in Japan, at department of chemistry, College of Science University of Mustansiriya .^{1}H NMR spectra were obtained with BRUKER spectrophotometer model ultra-shield at 300 MHZ in the University of Al-al-BaytAmman, Jordan. Using tetramethylsilane TMS as internal standard and $CDCl_3$, DMSO-d_6-as a solvents. The Mass spectra were recorded on SHIMADZU .model QP 1000EX using (SCL) mode, at department of chemistry, College of Science, University of Mustansiriya.

Synthesis of 2-(arylidene) hydrazine-1-carbothioamide (Schiff's bases) 2(a-f)

Aldehyde or Ketone 1(a-f) (0.02mol) was dissolved in (30ml) of ethanol at room temperature with stirring .After the solid compound was dissolved (2-3) drop of glacial acetic acid was added. The reaction mixture was stirred for (10min) then (1.82gm, 0.02mol) thiosemicarbazide was added. The reaction mixture was refluxed for (12hr).The precipitated solid obtained was filtered and washed with water. It was recrystallized from ethanol.

Synthesis of 1-((arylidene) amino) 2-thioxoimidazolidin-4-one 3(a-f):

2-(arylidene) hydrazine-1-carbothioamide 2(a-f) (0.01mol) was dissolved in (30ml) of ethanol with stirring .After the compounds dissolved (0.82gm, 0.01mol) of sodium acetate was added.

The reaction mixture was stirred for (20min), then (1.23 gm, 0.01 mol) of ethyl chloro acetate was add. The reaction mixture was refluxed for(14hr).The reaction mixture was allowed to stand at room temperature .The precipitated solid was filtered and recrystallized from ethanol to afford compounds 3(a-f).

Synthesis of4-(3-chloro aryl-4-oxo-1-(3-oxo-5-thioxo-2, 3-dihydroimidazo [5, 1-b] oxazol-6(5H)-yl) azetidin-2-yl) phenyl-2-chloroacetate 4(a-b)

1- ((arylidene) amino) 2- thioxoimidazolidin - 4- one3 (a-f) (0.005 mol) was dissolved in (25 ml) of dioxan at (0 ^{0}C) with stirring. After compounds were dissolved (0.5ml) of Et_3N was added .The reaction mixture was stirrd for (1hr), then (1.71gm, 0.015mol) of chloro acetyl chloride was added drop wise .The reaction mixture was heated for (42 hr) at (60 ^{0}C).The reaction mixture was allowed to stand at room temperature, then it was poured on crushed ice. The precipitated solid obtained was filtered and recrystallized from suitable solvent to afford compounds 4(a-b).

Synthesis of ((3-chloro aryl) azetidin-1-yl)-5-thioxo-5, 6-dihydroimidazo [5, 1-b] oxazol-3(2H)-one 5(c-f)

1- ((arylidene) amino) 2- thioxoimidazolidin - 4- one 3(a-f) (0.005mol) was dissolved in (25ml) of dioxan at (0^{0}C) with stirring. After compounds were dissolved (0.5ml) of Et_3N was added .The reaction mixture was stirrd for (1hr), then (1.14 gm, 0.01mol) of chloro acetyl chloride was added drop wise .The reaction mixture was heated for (24hr) at (60^{0}C).The reaction mixture was allowed to stand at room temperature, then it was poured on crushed ice .The precipitated solid obtained was filtered and recrystallized from suitable solvent to afford compounds 5(c-f).

Synthesis of 4-(((3-benzoyl-4-oxo-2-thioxoimidazolidin-1-yl) imino) aryl) phenyl benzoate 6(a-b)

1((arylidene)amino) 2- thioxoimidazolidin-4-one 3 (a-f) (0.005mol) was dissolved in (25 ml) of dioxan at room temperature with stirring .After compounds were dissolved (1ml) of Et_3N was added. The reaction mixture stirrd for (15 min), then (1.4 gm, 0.01 mol) of Benzoylchloride was added. The reaction mixture was refluxed (28 hr).The reaction mixture was precipitated with suitable solvent. The precipitated solid obtained was filtered and recrystallized from suitable solvent to afford compounds 6 (a-b).

Synthesis of 3-benzoyl-1-((arylidene) amino)-2-thioxoimidazolidin-4-one 7(c-e)

1((arylidene) amino) 2- thioxoimidazolidin-4-one 3 (a-f) (0.005mol) was dissolved in (25 ml) of dioxan at room temperature with stirring. After compounds were dissolved (1ml) of Et_3N was added. The reaction mixture stirrd for (15 min), then (0.7 gm, 0.005 mol) of Benzoylchloride was added .The reaction mixture was refluxed (14hr).The reaction mixture was precipitated with suitable solvent. The precipitated solid obtained was filtered and recrystallized from suitable solvent to afford compounds 7(c-e).

Synthesis of 3-benzoyl-1-((2-bromobenzylidene) amino)-2-thioxo-2, 3-dihydro-1H-imidazol-4-yl benzoate 8(f)

1((arylidene)amino)2-thioxoimidazolidin- 4-one 3 (a-f) (0.005 mol) was dissolved in(25ml) of dioxan at room temperature with stirring .After compounds were dissolved (1ml) of Et_3 N was added .The reaction mixture stirrd for (15 min), then (2.1 gm, 0.015 mol) of Benzoylchloride was added .The reaction mixture was refluxed (35 hr).The precipitated solid obtained was filtered and recrystallized from acetonto afford compound 8(f).

Synthesis of 4- (((3-acetyl-4-oxo- 2-thioxoimidazolidin - 1-yl) imino) aryl) phenyl acetate 9(a-b):

1-((arylidene)amino) 2-thioxoimidazolidin-4-one 3(a-f) (0.005 mol) was dissolved in (25 ml) of dioxan at room temperature with stirring . After compounds were dissolved (1ml) of Et3N was added .The reaction mixture stirrd for (15 min), then (0.78 gm, 0.01 mol) of Acetylchlorid was added .The reaction mixture was refluxed (24hr).It was allowed to stand at room temperature .The precipitated solid obtained was filtered and recrystallized from aceton to afford compounds 9(a-b).

Synthesis of 3- acetyl- 1-((arylidene) amino)-2- thioxoimidazolidin- 4- one 10(c-f)

1-((arylidene)amino) 2-thioxoimidazolidin-4-one 3(a-f) (0.005mol) was dissolved in (25 ml) of dioxan at room temperature with stirring. After compounds were dissolved (1ml) of Et3N was added.

The reaction mixture stirrd for (15 min) ,then (0.39 gm,0.005 mol) of Acetylchlorid was added .The reaction mixture was refluxed (14 hr).It was allowed to stand at room temperature. The precipitated solid obtained was filtered and recrystallized from suitable solvent to afford compounds10(c-f).

Spectral Data of Compounds

1-((4-hydroxybenzylidene) amino)-2-thioxoimidazolidin-4-one 3(a)

Yield 75% m.p 313-315 ^{0}C recrystallized from ethanol white solid compound was obtained; IR (cm^{-1}): 3227 (OH) phenol, 3220 (NH) imidazole ring, 3138 (CH=N), 3039 (C-H) ar, 2910, 2821 (CH) alp, 1683 (C=O) imidazole, 1645 (C=N) imine,1600,1581, 1514(C=C) ar,1082 (C=S) imidazole ring,831 (CH) para substituted; ^{1}H NMR (DMSO, 300MHz) δ 11.85 (s,1H,NH imidazole ring), 10.01 (s,1H,Ar-OH), 8.27 (s,1H,CH=N imine), 7.60-7.57 (d,2H,Ar-H),6.84-6.76 (d,2H,Ar-H), 4.01-3.87 (s,2H,CH_2 imidazole ring).

1-((1-(4-hydroxyphenyl) ethylidene) amino)-2-thioxoimidazolin-4-one 3(b)

Yield 90 % m.p 252-254^{0}C recrystallized from ethanol white solid compound was obtained; IR (cm^{-1}): 3308 (OH) phenol, 3225 (NH) imidazole ring, 3080 (C-H) ar, 2972, 2935 (C-H)alp,1685 (C=O)imidazole ring,1626 (C=N) imine, 1568,1512 (C=C)ar,1176 (C=S) imidazole ring, 840 (CH) para substituted ; ^{1}H NMR (DMSO, 300MHz) δ 10.49 (s, 1H,Ar-OH),7.83-7.80 (d,2H,Ar-H),6.77-6.74 (d,2H, Ar-H),4.40 (s, 2H,CH_2 imidazole ring),2.74 (s,3H,CH_3).

1-((1-(4-methoxyphenyl) ethylidene) amino)-2-thioxoimidazolidin-4-one 3(c)

Yield 95% m.p 180-182^{0}C recrystallized from ethanol light yellow solid compound was obtained; IR (cm^{-1}): 3236 (NH) imidazole ring, 3099 (C-H) ar, 2937, 2837 (C-H) alp, 1716 (C=O) imidazole ring, 1635(C=N) imine, 1606, 1591, 1508 (C=C) ar, 1178(C-O) ether,1020 (C=S) imidazole ring,837 (CH) para substituted; ^{1}H NMR (DMSO, 300MHz) δ 11.25 (s,1H,NH imidazole ring),7.91-7.78 (d,2H, Ar-H), 6.95-6.92 (d,2H,Ar-H),4.08 (s,2H, CH2 imidazole ring), 3.81(s,3H,OCH_3), 2.58 (s,3H,CH_3).

1-(((E)-3-phenylallylidene) amino)-2-thioxoimidazolidin-4-one 3(d)

Yield 85% m.p 230-232^{0}C recrystallized from ethanol light yellow solid compound was obtained; IR (cm^{-1}): 3200 (NH) imidazole ring,3170 (CH=N), 3057 (C-H) ar, 2960, 28 21(C H)alp,1703 (C=O) imidazole ring, 1683 (C=N) imine,1639 (C=C) alkene, 1606, 1568 (C=C) ar, 1172 (C=S) imidazole ring; ^{1}H NMR (DMSO, 300MHz) δ 11.95 (s,1H,NH imidazole ring), 8.33-8.20 (d,1H, (CH=N) imine), 7.42-7.37 (t,1H, (=CH) imine direction), 7.34-7.12 (m, 5H, Ar-H),7.05-7.04 (d,5H, (-CH=) aromatic ring direction) ,4.06 (s,2H,CH_2 imidazole ring).

1-((2-bromobenzylidene) amino)-2-thioxoimidazolidin-4-one 3(e)

Yield 91% m.p 255-257^{0}C recrystallized from ethanol white solid compound was obtained; IR (cm^{-1}): 3210 (NH) imidazole ring, 3175 (CH=N), 3063 (C-H) ar, 2935,2860 (C-H)alp,1716(C=O) imidazole ring, 1635(C=N) imine, 1579, 1556 (C=C)ar,1043 (C=S)im Idazole ring,750(C-Br); ^{1}H NMR (DMSO, 300MHz) δ 12.07(s,1H,NH imidazole ring),8.59 (s,1H, (CH=N) imine),7.49-7.38 signals refers to benzen aromatic groups, 4.0693(s,2H,CH_2 imidazole ring).Mass:(m/z) 294 with formula weight :($C_{10}H_8BrN_3OS$).

1-((4-(dimethylamino) benzylidene) amino) - 2-thioxoimidazolin- 4- one 3(f)

Yield 72% m.p 235-237^{0}C recrystallized from ethanol orange solid compound was obtained; IR (cm^{-1}): 3203 (NH) imidazole ring, 3149 (CH=N),3070(C-H) ar, 2966,2854, 2914,2804 (C-H)alp,1714 (C=O) imidazole ring, 1639(C=N) imine, 1604,1527 (C=C) ar,1120 (C=S) imidazole ring,812 (CH) para substituted; ^{1}H NMR (DMSO, 300MHz) δ 8.22 (S,1H, (CH=N)imine),7.57-7.54 (d,2H,Ar-H), 6.76-6.73 (d,2H,Ar-H),3.85 (s,2H, CH_2imidazole ring), 3.56(s,1H, (OH)tautomer with (NH),2.97 (s,6H,$N(CH_3)_2$).

4-(3-chloro-4-oxo-1-(3-oxo-5-thioxo-2, 3-dihydroimidazo [5, 1-b] oxazol-6(5H)-yl) azetidin-2-yl) phenyl 2-chloroacetate 4(a)

Yield 55% m.p 140-142^{0}C recrystallized from ethanol: H2O brown solid compound was obtained; IR (cm^{-1}): 3015(C-H)ar, 2928, 2860(C-H) alp,1772 (C=O) ester, 1732 (C=O) β-lactam ring,1666(C=O)oxazole ring,1600,1506 (C=C) ar,1016(C=S) imidazole ring; ^{1}H NMR (DMSO,300MHz) δ 7.78-7.72 (d,2H, Ar-H), 7.26-7.23 (d,2H,Ar-H),6.69 (s,1H,(OH) (tautomer. property) imidazole

ring), 4.87-4.71 (s,2H,$ClCH_2COO$) linked benzen aromatic ring,4.59-4.13 (m,4H, (CH_2) oxazole ring interfere with (CH-CHCl)ß-lactam ring.

4-(3-chloro-2-methyl- 4-oxo-5-thioxo-2,3-dihydroimidazo [5,1-b] oxazol- 6(5H)-yl) azetidin-2-yl)phenyl 2-chloroacetate 4(b)

Yield 61 % m.p 170-172^{0}C recrystallized from ethanol: H_2O brown solid compound was obtained; IR (cm^{-1}): 3076,3045 (C-H) ar, 2991, 2945(C-H) alp,1776 (C=O) ester,1728 (C=O)ß-lactam ring, 1681 (C=O) oxazole ring,1595,1558 (C=C) ar,1018 (C=S) imidazole ring; ^{1}H NMR (DMSO, 300MHz) δ 7.76-7.71(d, 2H,Ar-H),7. 28-7.23 (d,2H,Ar-H),4.53 (s, 2H, $ClCH_2COO$ interfere with ß-lactam proton), 4.35 (s,2H,(CH_2) oxazole ring),3.75 (s,1H, (=CH) imidazole ring,2.46 (s,3H,CH_3) linked ß-lactam ring.

6-(2-(2-bromophenyl)-3-chloro-4-oxoazetidin-1-yl)-5-thioxo-5,6-dihydroimidazo[5, 1-b] oxazol-3(2H)-one 5(e)

Yield 53% m.p 177-179^{0}C recrystallized from aceton:H_2O light brown solid compound was obtained; IR (cm^{-1}): 3061 (C-H) ar,2935,2881 (C-H) alp, 1724(C=O) ß-lactam ring,1638 (C=O) oxazole ring, 1604, 1525 (C=C) ar,1024 (C=S) imidazole ring,750 (C-Br); ^{1}H NMR (DMSO,300MHz) δ 7.67-7.35 (m,4H,Ar-H),6.99 (s,1H,(OH) (tautomer property) imidazole ring, 4.54-4.27 multi signals refers to (CO-CHCl) ß-lactam ring interfere with (CH)proton oxazole ring with proton imidazole ring,4.12 (s,1H, (CH-N) ß-lactam ring.

6-(3-chloro-2-(4-(dimethylamino) phenyl)-4-oxoazetidin-1-yl)-5-thioxo-5, 6 dihydroimidazo [5, 1-b] oxazol-3(2H)-one 5(f)

Yield 51% m.p 98-100^{0}C recrystallized from aceton:H_2O dark brown solid compound was obtained; IR (cm^{-1}): 3063(C-H) ar, 2949,2856, 2920, 2806 (C-H) alp,1718(C=O) new ß-lactam ring,1683 (C=O) imidazolering, 1585, 1560, 1521, 1508 (C=C) ar,1080 (C=S) imidazole ring, 812 (CH) para substituted; ^{1}H NMR (DMSO, 300MHz) δ 7.78-7.75(d,2H,Ar-H), 6.76- 6.73 (d, 2H, ArH), 4.86 (s,2H, CH_2oxazolering),4.39 (s,1H,(CHCl) ß-lactam ring, 3.79 (s, 1H,(CH=) imidazole ring) ,3.72 (s,1H,(CH-N) ß-lactam ring), 2.95 (s,6H,$N(CH_3)_2$).

4-(((3- benzoyl- 4- oxo- 2-thioxoimidazolidin-1-yl) imino) methyl) phenyl benzoate 6(a):

Yield 52% m.p 132-134^{0}C recrystallized from benzene brown solid compound was obtained; IR (cm^{-1}): 3172 (CH=N), 3086, 3039 (C-H) ar, 2978, 2953, 2848 (C-H) alp, 1728(C=O)ester, 1714(C=O) imidazole ring,1683(C=O)amide, 1633(C=N) imine, 1599, 1505 (C=C) ar, 1058(C=S) imidazole ring; ^{1}H NMR (DMSO, 300MHz) δ 8.37 (s,1H, (CH=N)imine),8.08-6.66 signals refers to benzene aromatic groups,3.95(s,2H,(CH_2)imidazole ring.

4-(1-((3- benzoyl- 4- oxo- 2-thioxoimidazolidin- 1- yl) imino) ethyl) phenyl benzoate 6(b)

Yield 66% m.p 169-171^{0}C recrystallized from ethanol orange solid compound was obtained; IR (cm^{-1}): 3070, 3026 (C-H) ar, 2944, 2883 (C-H) alp, 1730 (C=O) ester, 1715 (C=O) imidazole ring, 1697(C=O) amide, 1614 (C=N) imine, 1600, 1589 (C=C) ar,1060 (C=S) imidazole ring; ^{1}H NMR (DMSO, 300MHz) δ 8.19-7.28 signals refers to benzene aromatic groups, 3.79 (s,2H,(CH_2) imidazole ring,2.61 (s,3H,CH_3). Mass: (m/z) 457with formula weight :($C_{25}H_{21}N_3OS$).

3-benzoyl- 1-((4- (dimethylamino) benzylidene) amino)- 2-thioxoimidazolidin- 4-one 7(e)

Yield 67% m.p 71-73^{0}C recrystallized from ethanol: H2O dark brown solid compound was obtained; IR (cm^{-1}): 3111(CH=N), 3057(C-H) ar,2972, 2924, 2899, 2860, 2810 (C-H) alp, 1710 (C=O) imidazole ring, 1685 (C=O) amide, 1637 (C=N)imine,1606, 1526(C=C) ar, 1060(C=S) imidazole ring; ^{1}H NMR (DMSO, 300 MHz) δ 8.50(s,1H,(CH=N) imine) 7.36-6.65 signals refers to benzene aromatic groups,3.95 (s,2H, (CH_2) imidazole ring,3.37 (s,6H,($N(CH_3)_2$).

3-benzoyl- 1- ((2- bromobenzylidene) amino)-2- thioxo-2, 3- dihydro-1H-imidazol- 4-yl benzoate 8(f)

Yield 58% m.p 166-168^{0}C recrystallized from aceton dark brown solid compound was obtained; IR (cm^{-1}):3151(CH=N), 3055 (C-H) ar, 2949, 2933, 2812 (C-H) alp, 1726 (C=O) ester, 1639 (C=O) amide, 1581, 1521 (C=C) ar,1022 (C=S) imidazole ring,750 (C-Br);^{1}H NMR (DMSO, 300MHz) δ 8.51 (s,1H, (CH=N) imine), 7.60-7.31 signals refers to benzene aromatic groups, 3.97 (s,1H, (CH=) imidazole ring).

4-(1-((3- acetyl- 4- oxo- 2- thioxoimidazolidin-1-yl) imino) ethyl) phenyl acetate 9(b)

Yield 68% m.p 176-178^{0}C recrystallized from ethanol white solid compound was obtained; IR (cm^{-1}):3093, 3043(C-H) ar, 2987, 2943, 2893(C-H) alp, 1751(C=O) ester, 1714 (C=O) imidazole ring, 1683 (C=O) amide, 1616 (C=N) imine, 1600, 1579 (C=C) ar, 1016 (C=S) imidazole ring; ^{1}H NMR (DMSO, 300MHz) δ 7.84-7.81 (d, 2H, Ar-H), 7.18-7.05 (d,2H, Ar-H),3.82 (s, 2H, (CH_2) imidazole ring), 2.39 (s,3H, (CH_3COO) group), 2.26 (s,6H,(CH_3CON) interfere with (CH_3C=N) group). Mass:(m/z) 332 with formula weight: ($C_{15}H_{15}N_3OS$).

3-acetyl-1-((1-(4-methoxyphenyl) ethylidene) amino)-2-thioxoimidazolidin-4-one 10(c)

Yield 63% m.p 104-106^{0}C recrystallized from ethanol brown solid compound was obtained ; IR (cm^{-1}):3074, 3012 (C-H)ar, 2982, 2953, 2924, 2835 (C-H) alp,1701(C=O) imidazole ring, 1689 (C=O) amide,1649 (C=N) imine,1602, 1514 (C=C) ar,1030 (C=S) imidazole ring,1182(C-O) ether; ^{1}H NMR (DMSO, 300MHz) δ 7.31-7.28 (d,2H,Ar-H), 6.86-6.83 (d,2H,Ar-H), 4.26 (s, 2H, (CH_2) imidazole ring), 3.67 (s, 3H, (CH_3O-C_6H_4)),2.16 (s,3H, (CH_3CO) amide), 1.98-1.15 (s,3H, (CH_3C=N)).

3- acetyl- 1- ((4-dimethylamino) benzylidene) amino)-2-thioxoimidazolidin- 4-one 10(f)

Yield 72% m.p 105-107^{0}C recrystallized from aceton orange solid compound was obtained; IR (cm^{-1}): 3105 (CH=N), 3026(C-H) ar, 2947, 2920, 2858, 2816 (C-H) alp, 1718 (C=O)imidazole ring, 1676(C=O) amide,1610 (C=N) imine, 1583, 1531 (C=C) ar,1080 (C=S) imidazole ring; ^{1}H NMR (DMSO,300 MHz) δ 8.05-8.00 (s,1H, (CH=N) imine),7.46-7.43(d,2H,Ar-H), 6.71-6.68 (d,2H, Ar-H), 3.64 (s,2H, (CH2) imidazole ring 3.05 (s,6H, (N (CH_3)$_2$), 2.46(s,3H, (CH_3CO) amide). Mass :(m/z) 304 with formula weight:($C_{14}H_{16}N_4O_2S$).

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